Reviewer's report

Title: Kidney disease is associated with early development of subcutaneous tophi in people with gout

Version: 1
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Reviewer: Eswar Krishnan

Reviewer's report:

Thank you for giving an opportunity to review this manuscript that examines the Association between kidney disease and subcutaneous tophus among people with gout. I enjoyed reading this paper which was pithy and well written. The data are excellent given the detailed clinical phenotypic information that are available.

The authors have enrolled patients with gout for less than 10 years, assessed their subcutaneous tophus status, and performed cross-sectional analysis with several variables including kidney disease variable. The document that that patients with gout and tophi had more symptoms of gout than those with gout only. They observe that kidney disease, as measured by reduced creatinine clearance, were statistically correlated with earlier presentation of subcutis tophii-ergo, kidney disease is a risk factor for earlier development of subcutaneous tophus.

Major Revisions

From a statistical perspective, there are two major fixable issues

1. Including creatinine clearance in a model that already has age, sex, and other variables is problematic since creatinine clearance is calculated using age weight and gender. You may be double adjusting. Consider dropping age and gender in the multivariable odds ratio presented in table 3. This can be provided as an additional column or can replace the present multivariable model.

2. Using count variable, namely the number of tophi, as a dependent variable in multiple regression analysis is questionable if not incorrect. A simple Google search will illustrate this. The correct statistical model to be used is either Poisson regression or negative binomial regression models. Either of them would provide relative risk estimates. Furthermore it may be important to examine the association between the number of tophi and independent variables among those who have at least one tophus.

3. Was there a difference in the Association between kidney disease and gouty tophi between the two genders? Have you examined an interaction time in the regression model?

4. Lastly, being a cross-sectional study consider stating the results as cautiously as possible.

Discretionary Revisions
The paper could be strengthened in the following ways:

1. The critical variable used in the study is the disease duration. This duration is calculated as the time elapsed since the first gouty attack. Regardless of the specific case definition used to determine attack (self-report, self-reported physician diagnosis, or physician diagnosis that has been documented) it will be important to spell it out.

2. In the discussion section it may be worthwhile to add a sentence or two to mention that in many individuals, tophus can precede the onset of clinical gouty arthritis.

3. In the paragraph mentioning their limitations of the study, the authors state “estimation of disease duration may be difficult in gout, especially since tophi may be undetected by both the individual and healthcare professionals. However the definition used as consistent with virtually all studies of gout…”. I thought it was a little confusing since detection of tophi or otherwise is not required for a diagnosis of gout. Please rephrase the sentence.

4. The title of the paper talks about kidney disease being associated with early development of subcutaneous tophi. However going through the methods section I do not see a definition of kidney disease. I suggest you provide a definition for kidney disease so that your results can be tied into the title or change the title to reflect that produced creatinine clearance is associated with tophi. I recommend the latter approach.

5. Since this is a kidney function paper, would the results be significantly different if he had used the CKD-EPI equations?

6. In the results section, the authors describe the differences in the number of swollen and tender joints. Given that the average age of people with tophi is 64, how much of those active joints could be attributed to osteoarthritis? Please include two or three sentences to address this in the discussion section; I think it is important because your central thesis is that those with tophi have more active joints.

7. It is surprising to see that obesity measures were not statistically associated with tophaceous gout. This merits a comment from the authors

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests: NO